REMARKS

Applicants thank former Examiner Rae for acknowledging their claim amendments and their support for the amended claims, and for reconsidering and withdrawing the § 112 (written description) and § 102 (anticipation) rejections in the context of those amended claims.

Applicants thank Examiner Purdy for the courtesies extended during the October 23, 2009 interview. At the interview, the various rejections in the July 7, 2009 Final Office Action and the cited Ohuchida et al., U.S. Patent 7,176,240 ("Ohuchida") and Sramek et al., Opin. Invest. Drugs 2002: 741-752 ("Sramek") documents were discussed. No agreement was reached. No exhibits were shown (applicants provided to the Examiner an outline of the issues and their responses in advance of the interview), and no demonstrations were conducted.

Amendment of Claims

Applicants have amended claim 44, the only independent claim, to clarify that the subject treated in the claimed method is a subject in need of such treatment. This amendment responds to a discussion had at the end of the October 23, 2009 interview. Applicants have also amended claim 53 to be consistent with amended claim 44.

These amendments are proper under 37 C.F.R. § 1.116. They address an issue of form first raised at the interview and they present the claims in a form for allowance, or at least in a better form for consideration or appeal. Applicants request entry of the claim amendments.

Rejection under 35 U.S.C. § 103(a): Obviousness

Claims 44 and 53 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Ohuchida in view of Sramek. The Examiner contends: (1) that Ohuchida refers to treating neurodegenerative diseases, including Alzheimer's Disease ("AD"), using, *inter alia*, pentanoic acid derivatives, including valproic acid, and (2) that Sramek recites that drugs used to treat AD are also likely to be used to treat Mild Cognitive Impairment ("MCI"). The Examiner, thus, argues that applicants' claims for treating MCI with valproic acid derivatives are obvious. The Examiner further contends that because Ohuchida refers to treating numerous diseases, including AD, with pentanoic acid derivatives, including valproic acid, and because Sramek refers to an up to 15% per year conversion rate of MCI to AD, there is a sufficient nexus between MCI and AD, such that the skilled worker, at the filing date of the application, would have reasonably expected treating MCI with valproic acid derivatives to be successful. Applicants traverse.

As explained in applicants' April 1, 2009 Amendment and Response to the November 7, 2008 Office Action and at the October 23, 3009 interview, Sramek refers only to *exploring* AD treatment strategies in MCI (p. 742, paragraph bridging the two columns, emphasis added). In fact, Sramek recites only that it is "*plausible that at least some* AD therapeutics will be just as efficacious, if not more, in the treatment of MCI" (p. 745, second column, emphasis added). Sramek, however, also acknowledges that "whether or not these compounds [AD therapeutics] will prove effective in MCI *remains to be determined*" (p. 745, second column, emphasis added). Thus, Sramek is no more than a research plan that hopes to find a possible treatment for MCI from among AD

treatment strategies and even then the plan is based on there being an effective treatment for AD. It is in no way a teaching with a reasonable expectation of success that any specific AD treatment strategy, much less valproic acid derivatives, will be effective in treating MCI. Thus, Examiner Rae's contention fails the "common sense" approach of the Court in KSR. In fact, the only common sense conclusion is that Ohuchida and Sramek provide no reasonable expectation that valproic acid derivatives are useful in treating MCI.

So what does Sramek actually tell the skilled worker to do in the context of Examiner Rae's asserted combination of Ohuchida and Sramek? Sramek tells the skilled worker to find a compound or treatment strategy that actually works to treat AD. Indeed, Sramek says repeatedly that a demonstration of an agent's effectiveness in AD is needed before it is even tried in MCI. *See*, e.g., p. 746, section 5.2, last sentence and p. 749, first full paragraph, last sentence. Only then does Sramek say that the compound or treatment strategy might be tried to see if it would be effective in treating MCI. However, Sramek acknowledges over and over again that there is no reasonable expectation that the AD compounds or treatment strategies will be successful in treating MCI.

On that basis alone, Examiner Rae's Ohuchida/Sramek combination fails. In fact, the documents cannot even be combined because Ohuchida never demonstrates that valproic acid derivatives are effective in treating AD and Sramek requires a successful AD treatment before even looking to possibly treat MCI.

First and foremost, AD is only one of a myriad of "neurodegenerative" diseases that Ohuchida lists as possible candidates for treatment with pentanoic acid derivatives. Just as importantly, Ohuchida points only to data suggesting that valproate improved astrocyte functions and suppressed neuron death *in vitro*. Neither demonstrates that valproic acid derivatives are useful in treating AD. Sramek, by contrast, requires starting with a compound or treatment strategy that is successful in treating AD to test if it is effective in treating MCI. Ohuchida does not demonstrate that valproate is such a compound. For this reason alone, the skilled worker, with Sramek in hand, would never have even tried valproic acid derivatives to treat MCI.

Examiner Rae's Ohuchida/Sramek "combination" also fails for another reason. Even if the skilled worker were to have viewed Ohuchida's in vitro tests as relevant to the effective treatment of AD (which they are not), the skilled worker would still have had no reasonable expectation that valproate would be effective in treating MCI. Indeed, as explained above, Sramek repeatedly acknowledges that whether or not compounds that successfully treat AD will also treat MCI "remains to be determined".

In their April 1, 2009 Amendment and Response, applicants demonstrated by pointing to actual verifiable facts how tenuous and unreasonable Sramek's "to be determined" caveat really was.

First, within Sramek's five classes of AD compounds, the only class of compounds that Sramek reported as useful in treating AD (and even then only in effecting symptomatic improvement) was acetylcholinesterase inhibitors ("AChEIs"). That success was not enough for Sramek to suggest that the AChEIs would reasonably be

expected to effectively treat MCI, or even to improve its symptoms. Rather, Sramek reported only that the effects of AChEIs in MCI were being tested in the clinic. Subsequent reports have provided the results of those trials. The AChEIs were not effective in treating MCI. *See* Peterson (Exhibit B, April 1, 2009 Amendment and Response), p. 2385, second column.

Second, members of the other classes of compounds reported by Sramek to have failed or to be still under investigation for treating AD, and thus, not even candidates to try in MCI, were nonetheless (and directly contrary to Sramek's "teachings") tested in MCI. They all failed. *See* Thal (the Abstract), Peterson (the Conclusions section, p. 2382 and Table 2) and Allain (the Abstract) (Exhibits A, B and C, respectively, from applicants' April 1, 2009 Amendment and Response).

In response to this specific evidence of repeated failures of Sramek's classes of compounds to treat MCI, Examiner Rae contends that such failures are not relevant to the alleged obviousness of treating MCI with valproic acid derivatives because the compounds that failed are structurally unrelated to valproate, and that therefore, valproic acid derivatives would still have been reasonably expected to successfully treat MCI, the other failures notwithstanding. Applicants traverse.

Structural relatedness is not the relevant issue to a skilled worker's understanding of Sramek. The issue is whether or not compounds shown to be useful to treat AD (e.g., allegedly pentanoic acid derivatives according to Ohuchida) would be reasonably expected to be successful in treating MCI. As demonstrated by the above actual clinical evidence, and further in view of Sramek's own statements and admissions, they would not have been.

Moreover, subsequent reports have demonstrated that, contrary to the fundamental assumptions underlying Examiner Rae's combination of Ohuchida and Sramek, valproate is not even useful in treating AD. *See*, e.g., Herrmann et al, The Canadian Journal of Psychiatry (2007) 52: 630-646 (Exhibit D), pages 630 and 636-637; Tariot et al., Am. J. Geriatr. Psychiatry (2005) 13: 942-49 (Exhibit E), Abstract and Conclusion. Indeed, at the July, 2009 International Conference on Alzheimer's Disease (ICAD), it was reported that chronic valproate treatment of AD patients had no effect on the clinical progression of AD, and further had no effect on any secondary measures of the disease, including behavior, cognition, memory or global status. *See* Tariot et al., Alzheimer's Disease Cooperative Study: Chronic Valproate Therapy To Attenuate The Clinical Progression Of Alzheimer's Disease (ICAD 2009) (Exhibit F). Others have also reported that, while valproate improved agitation (a symptom of dementia and AD in some patients), it was not useful in treating AD itself. Further, it did not improve cognition – a hallmark of any MCI treatment. *See* Tariot et al., Current Therapeutic Research (2001) 62: 51-67 (Exhibit G), Table 2 (p. 63); Porsteinsson et al., Am. J. Geriatr. Psychiatry (2001) 9: 58-66 (Exhibit H), pp. 55 and 59. Thus, valproate, having

failed to treat AD, and having even failed to improve cognitive function in AD patients, would not have been reasonably expected to be effective in treating MCI. Therefore, for this reason and the actual clinical evidence, Examiner Rae's combination fails to render the amended claims obvious.

For all of the above reasons, applicants request that Examiner Purdy reconsider and withdraw the last remaining obviousness rejection.

CONCLUSION

Applicants request favorable consideration of and early allowance of amended claims 44 and 53. The Examiner is invited to telephone the undersigned to discuss any issue pertaining to this response or amended claims 44 and 53.

Respectfully submitted,

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